

<b>Antagonists</b> Argos Melanogasta	PGYRYLFAQSP-LTRLRQQRKQPKLFTVRKQREFLDEVNINSIQGPK---GHRQPSHHTQSG-	Drosophila
	IEKLKEAKCKD-----YCHHNATCHVEVIFRED---RVSAVVPSCGHPQGWETRGDRHYVQAF-	C. elegans
<b>Agonists</b> Lin-3 Vein Gurken Spitz Keren	DRSASGIPCN--FD--YGFHNGTGRMIPDIN-----EVY---GRQPTETFGNCKENKWPDSR-	D. Melanogasta
	ETEIQMLPQSEAYNTSFLNGGHCFOHPMVNN-----TVFHSGLGVNDYDGERCAAYKSWNGD-	D. Melanogasta
	NITFPTYKCPETFDAWYCLNDAHFAVKIADL-----PVYS--GECALGFMCORCEYKEIDNT-	D. Melanogasta
	NVTFPIFACPTTYVAVYCLNDGTCTFTVKIHNE-----ILYN--GECALGFMCORCEYKEIDGS-	D. Melanogasta
	TGTSHLVKCAEKEKT-FGVNGGCFMVKDLS-----NPSRYLCCKQPGFTGARGTENVPMKV-	Homo sapiens
NRG1_alpha NRG1_beta NRG2_alpha NRG2_beta NRG3 NRG4	TGTSHLVKCAEKEKT-FGVNGGCFMVKDLS-----NPSRYLCCKQPGFTGDRCONVVMASF-	Homo sapiens
	SWSGHARKCNETAKS-YGVNGGVYYIEGIN-----QLS----CKQPNGFFGQRCLEKLPRL-	Homo sapiens
	SWSGHARKCNETAKS-YGVNGGVYYIEGIN-----QLS----CKQPVGYTGDRQQQFAMVNF-	Homo sapiens
	ERSEHFKPCRDKDLA-YCLNDGECFVIETLTG-----SHK--HRCQKEGYQGVRRDQ-FLPKTD	Homo sapiens
	MPTDHEEPQGPSHKS-FCLNGGLCYVIPTIP-----SP----FCRCVENYTGARCEVFLPGS-	Homo sapiens
EGF TGF_alpha Betacellulin Amphiregulin HB-EGF Epiregulin Epigen	SVRNSDSECPPLSHDG-YCLHDGVCMYTEALD-----KYA---GNCVVGYYIGERCYRDLKMW-	Homo sapiens
	AVVSHFNDCPDSHTQ-FCFH-GTGRFLVOED-----KPA---CVCHSGYVGARCEHADLLAV-	Homo sapiens
	KRKGHFSRCQPKQYKH-YCIK-GRGRFVVAEQ-----TPS---GVDEGYIGARCEVDLFLYL-	Homo sapiens
	RNRKKNPQNAEFON-FOIH-GECKYIEHLE-----AVT---SKQQEEYFGARCEGSEKSMKTH-	Homo sapiens
	GLGKKRDPCLRKYKD-FOIH-GECKYIEHLE-----APS---GIDHPGYHGERCHGLSLPVE-	Homo sapiens
Conserved cysteine #:	VAQVSITKSSDMNG-YCLH-GQCIYLVDMSE-----QNY---GRCEVGYTGARCEHFLTVH-	Homo sapiens
	VALKFSHPQLEDHNS-YQIN-GAQAFHHLK-----QAI---GRQFTGYTGARCEHFLTVH-	Mus musculus

Figure 1

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Dros._melanogaster -----MPTTLMLLPMLLLLLTAAAVAVGGTRLPLEVFEITPTTS--TADKHKSL
Dros._virilis      MASIRAHSLLLLLRLMLPLPLLLLLMLTGGAQSTRPLEVYELTPTASADSDAKHKSL
Musca_domestica    -----MLSLTIIFMLATHIINAGYSTRLPLEVYELTPNAAGGTDLKHKNL
                      :*. :*: . .*****;*:*: : :*.

Dros._melanogaster QYTVVYDAK-----DISG-----AAAATG-----VASSTVKPATEQLTVVSISSTAAA
Dros._virilis      EY-AIYDPK-----ELTGAPKAAAAAAATT-----TTSSTARPSSEKPLAIAVVISAE
Musca_domestica    EYSTINGSGGQHFLAINGRSKQHVSAAMEEPELKMLSSHDSKAAATKTLTVSSMGTPSA
                      :* . : . :.* :** :* : : : : : . :

Dros._melanogaster EKDLAES-----RRHARQMLQKQQQ-----HRSIIGG---K
Dros._virilis      QQQQQQSELEPATQ-----AGRRARQMLQQQHR-----LSSSSSSSSNK
Musca_domestica    AATTTSTSTATATATTNQLDRRRSRQMLDIMQKNHHDQTGNHKLPPVLSSGEGAATG
                      * :*:** : : *

Dros._melanogaster HGD--RDVRILYQVGDSEEDLPVCAFNAVCSKIDLYETPWIERQCRCPESNRMPNNVIIH
Dros._virilis      HAHSVKDLRILYQVGDSEADLPVCAFNAVCSKIDLYETPWIERQCRCPESNRMPNNVIVH
Musca_domestica    ASHSQKDVRLYQVGNSEDDLPICAFNAVCSKIDLYETPWIERQCRCPAVNRSPEIHH
                      .. :*:*****;* ***:*****:***** * * : *
                      <----->
                      A1 domain

Dros._melanogaster HHSHSSGSVDS--LKRYNYYEREKMMQHKR---MLLGEF---QDKKFESLHMKKLMQKLG
Dros._virilis      HHEHPHGTMSG-QKYRSYYEKEKLLQHKR---LL-----DKKYESLHLKLMQKLG
Musca_domestica    HHKETASHSNHNSEKYHTFYEHSLAHQOQNKHLLDAASVFGDKKFDNLHLKLMHKLK
                      **... . ***:***: : : : :** ***:***:***:**

Dros._melanogaster AVYEDDL-----DHLDQS---PDYNDALP--YAEVQDNEFP-----RGSAHM
Dros._virilis      AVYEDDLQLPSAGDYVERS---PDYNEALPPAYEELADNELPQ-----APARSATHM
Musca_domestica    AVYEDDLNLPDYHRHEETNSALDDSEATLYYADEIKDNEFFAHFAMKRQHLYSNTPHM
                      ***** . : : * * : * : * : : : : : : : : : : : : : : : : :

Dros._melanogaster RHSGHRG-SKEPATTFIGGCPSSLGVEDGHTIADKTRHYKMCQPVHKLFPVCTHFRDYTWT
Dros._virilis      RHSGHRG-LKE-AVSFIGGCPSNLGVEDGHTIADKTRHYKLCQPVHKLFPVCKHFRDYTWT
Musca_domestica    RHSGHTGGHGGKISYIGGCPSLGIEDGHTIADKTRHYKMCQPVHRLFPVCRHFRDYTWT
                      ***** * : :*****;* ***:*****:*****:*****
                      <----->
                      A2 domain

Dros._melanogaster LTTAAELNVTEQIVHCRCRPNRSVTYLTKEPIGNGSPGYRYLFACSPLTRLRCQKQKPK
Dros._virilis      LTTAAELNVTEQIVHCRCRPNRSVTYLAKEPVPNSSTAYRYLFACSPLTRLRCQKQKPK
Musca_domestica    LTTSPENMTTEQIVHCRCRPNRSVTYLTKEPSEDGNGGYKYLFACSPLTRFRQKQKPK
                      ***:*. :*.***:*****:*****:*** ... :*:*****:*****
                      <----->
                      A2 (continued)
                      EGF domain

Dros._melanogaster LFTVRKRQEFLEVNINSLCCPKGHRCPSSHHTQSGVIAGESFLEDNIQTYSGYCMAND
Dros._virilis      LFTVRKRQEFLEVNINSLCCPKGHRCPSSHHTQSGVIAGESFLEDNIQTYSGYCMAND
Musca_domestica    LFTVRKRQEFIDEVNINALCCPKGHCPSHHTQSGVIAGETFLEDNIQTYSGYCMVND
                      *****:*****:*****:*****:*****:*****
                      <----->
                      EGF domain (continued)

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Figure 2

	Sequence ID #	
NRG1_alpha	1	TGTSHLVKAEKEKTCVNGGECFMVKDLSNPSRYLCKCQPGFTGARCTENVPMKV
NRG1_beta	2	TGTSHLVKAEKEKTCVNGGECFMVKDLSNPSRYLCKCPNEFTGDRQCQNYVMASF
NRG2_alpha	3	SWSGHARKCNETAKSYCVNGGVCYYIEGINQLS—CKCPNGFFGQRCLEKLPRL
NRG2_beta	4	SWSGHARKCNETAKSYCVNGGVCYYIEGINQLS—CKCPVGYTGDRCCQCFAMVNF
NRG3	5	ERSEHFKPCRDKDLAYCLNDGECFVIETLTGSHK-HCRCCKEGYQGVRCDDQFLPKTD
NRG4	6	MPTDHEEPCGSPSHKSFCLNGGLCYVIPTIP-SP-FORCVENYTGARCEEVFLPGS
EGF	7	SVRNSDSECPLSHDGYCLHDGVCMYEALDKYA—CNCVVGYIGERCQYRDLKWW
TGF_alpha	8	AVVSHFNDCPDSTHTQCFH-GTCRFLVQEDKPA—CVCHSGYVGARCEHADLLAV
Betacellulin	9	KRKGFHSRCPKQYKHYCIK-GRCRFVVAEQTPS—CVCDEGYIGARCERVDLFYL
Amphiregulin	10	RNRKKKNPCNAEFQNFCH-GECKYIEHLEAVT—CKCQQYFGERCGEKSMTKTH
HB-EGF	11	GLGKKRDPCLRKYKDFCIH-GECKYVKELRAPS—CICHPGYHGERCHGSLPVE
Epiregulin	12	VAQVSITKCSSDMNGYCLH-GQCIYLVDMSONY—CRCEVGYTGVRCEHFFLT VH
Epigen	13	VALKFSHPCLIEDHNSYCIN-GACAFHHELKQAI—CRCTGYTGQRCEHLLTTSY
		* : * : * : * : * : * : * : * : * : * : * : * : * : * : *

Figure 3

		Sequence ID #	4/8
<b>HUMAN</b>			
NRG1_alpha		14	
NRG1_beta		15	
Translated genomic locus		73, 128	
	<div> <div> <div>&lt;-----</div> <div>Exon A</div> <div>-----&gt;</div> </div> <div> <div>-----&gt;</div> <div>Exon B</div> <div>-----&gt;</div> </div> </div>		
	TGTSHLVKCAFEKKTFCVNGGECFMVKDLSNPSRYLCKCQPGFTGARTENVPMKVO...		
	TGTSHLVKCAFEKKTFCVNGGECFMVKDLSNPSRYLCKCPNEFTGDRCONYVMASFY...		
	TGTSHLVKCAFEKKTFCVNGGECFMVKDLSNPSRYLCK*		
NRG2_alpha		16	
NRG2_beta		17	
Translated genomic locus		74, 129	
	SWSGHARKQNETAKSYCVNGGVCYYIEGINQLS--CKCPNGFFGQRCLEKLPRLYL...		
	SWSGHARKQNETAKSYCVNGGVCYYIEGINQLS--CKCPVGYTGDRCCQFAMVNFY...		
	SWSGHARKQNETAKSYCVNGGVCYYIEGINQLS--CK*		
NRG3		18	
Translated genomic locus		75, 130	
	ERSEHFKPRDKDLAYCLNDGECFVETLTGSH-KHCKCKEGYQGVRCDO-FLPKTD....		
	ERSEHFKPRDKDLAYCLNDGECFVETLTGSH-KHCR*		
NRG4		19	
Translated genomic locus		76, 131	
	MPTDHEPFGPSHKSFCLNGGLGVVIPTIPSPF--GRQVENYTGARCEEVFLPGSS....		
	MPTDHEPFGPSHKSFCLNGGLGVVIPTIPSPF--GR*		
EGF		20	
Translated genomic locus		77, 132	
	....SVRNSDECPLSHDGVCCLHDGVCMYIEALDKYA--CNQVVGVIIGERCQYRDLKWWE....		
	SVRNSDECPLSHDGVCCLHDGVCMYIEALDKYA--CK*		
TGF_alpha		21	
Translated genomic locus		78, 133	
	AVVSHFNDCPDSHTQFCFH-GTCRFLVOEDKPA--CVCHSGYVGARCEHADLLAV....		
	AVVSHFNDCPDSHTQFCFH-GTCRFLVOEDKPA--CV*		
Betacellulin		22	
Translated genomic locus		79, 134	
	KRKGFHSRCPKQYKHVCK-KRCRFWAEQTPS--CVCDEGYIGARCEKRVDFLYLR....		
	KRKGFHSRCPKQYKHVCK-KRCRFWAEQTPS--CV*		

Figure 4

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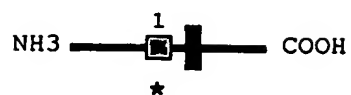
Amphiregulin Translated genomic locus	<p> RNRKKKNPCNAEFQNECIH-GECKYIEHLEAVT-CKCQOEYFGERGCEKSMKTHS....  RNRKKKNPCNAEFQNECIH-GECKYIEHLEAVT-CK* </p>	23 80, 135
HB-EGF Translated genomic locus	<p> GLGKKRDPCLRKYKDFCIH-GECKYVKELRAPSL-CHHPGYHGERGCHGLSLPVEN....  GLGKKRDPCLRKYKDFCIH-GECKYVKELRAPSL-CM* </p>	24 81, 136
Epiregulin Translated genomic locus	<p> VAQVSITKCSSDMNGYCLH-GOCIYLVDMSONY-CCRCEVGYTGVRCEHFFLTVHQ....  VAQVSITKCSSDMNGYCLH-GOCIYLVDMSONY-CR* </p>	25 82, 137
Epigen(Mouse) Trans. mouse genomic locus Trans. human genomic locus	<p> VALKFSHPCELEDHNSYICIN-GACAFHHEIKQAT-CCRCEFTGYTGORCEHLLTTSYA....  VALKFSHPCELEDHNSYICIN-GACAFHHEIKQAT-CR*  IALKFSHLCLEDHNSYICIN-GACAFHHELEKAT-CR* </p>	26 83, 138 84, 139

Figure 4 (continued)

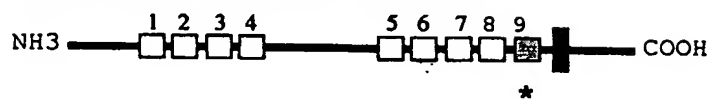
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## i) TGF-alpha



## ii) Epidermal Growth Factor



## iii) Notch 1

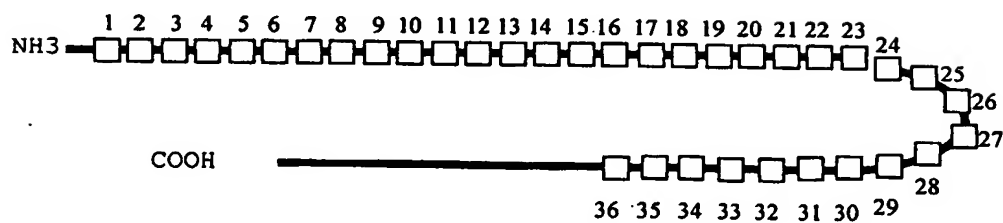


Figure 5A

i) TGF alpha		Sequence ID #
EGF DOMAIN NUMBER		
1.	EGF_47_82 *	72
-----SEQUENCE-----		
QBSHTQVCE-HGT-GRFAVQEDKPAVCHSG--YVGAR--TC		
ii) EPIDERMAL GROWTH FACTOR		Sequence ID #
EGF DOMAIN NUMBER		
1.	EGF_318_354	27
2.	EGF_360_395	28
3.	EGF_401_436	29
4.	EGF_439-476	30
5.	EGF_745_780	31
6.	EGF_835_868	32
7.	EGF_874_910	33
8.	EGF_916_951	34
9.	EGF_976_1012 *	35
-----SEQUENCE-----		
EKLR-KENCS--STVCGDLE--QSHLCMGATGYALSRDRKYG		
CALW-NHGG--TEGGKNTLP--GSYYCTCPVGFVWLPDGRKG		
EPRN-VSEC--SHDGVMTS--EGPICTGPDGSMTERDGKTC		
SSSPDNGGCS--QLCVPLSP--VSWPCDPRGMDLDELKSC		
QLYQFNGGCT--EHLCKGGL--GTAWGSCREGEMKASDGKTC		
GAPV--COS-MYARCTSEC--EDATCQGLKG--PAGDGKTC		
CEMG-VLVEPPASSKGINLB--GGVCRGSEC--YQGDGPHG		
EQLG-VHSCGENAS--GINTLP--GGVCMCAGR--LSEPGHIC		
EPLSHDGLCL-HDGVCMALDRAACN--CVVG--YIGER--C		
iii) Notch1		Sequence ID #
EGF DOMAIN NUMBER		
1.	EGF_24_57	36
2.	EGF_63_98	37
3.	EGF_106_138	38
4.	EGF_144_175	39
5.	EGF_182_215	40
6.	EGF_222_254	41
7.	EGF_261_292	42
8.	EGF_299_332	43
9.	EGF_339_370	44
10.	EGF_376_409	45
11.	EGF_416_449	46
12.	EGF_456_487	47
13.	EGF_494_525	48
14.	EGF_532_563	49
15.	EGF_570_600	50
16.	EGF_607_638	51
17.	EGF_645_675	52
18.	EGF_682_713	53
19.	EGF_720_750	54
20.	EGF_757_788	55
21.	EGF_795_826	56
22.	EGF_833_867	57
23.	EGF_874_905	58
24.	EGF_912_943	59
25.	EGF_950_981	60
26.	EGF_988_1019	61
27.	EGF_1026_1057	62
28.	EGF_1064_1095	63
29.	EGF_1102_1143	64
30.	EGF_1150_1181	65
31.	EGF_1188_1219	66
32.	EGF_1226_1265	67
33.	EGF_1272_1305	68
34.	EGF_1312_1346	69
35.	EGF_1353_1384	70
36.	EGF_1392_1426	71
-----SEQUENCE-----		
CSQ-----PGETCLNGGKCEAANGTE-----ACVCG-GAFVGP		
GKS--TPCKNACTCH-VVDRRGVADYACSCA--EGFSGP		
GHL--NFCRNGGTCG--LTLT--LYKCRCP--PGWSGKSC		
CAS--NPGANGGQOC--TP--FASVYQHCP--ESTHGETC		
CGO--KPRLCRHGCTGHNEVGSY--FRCVER--ATHGTGNC		
ESLSP--CONGGTRETGDV--THHCAGL--PGFTGQNC		
SPGNN--GNGGCAOV--DGVN--TYNCECP--PEWTGOYC		
CQL--MPNACONGCTCHNTHGGY--NCVCV--NGMTGEDC		
CAS--NAGEHCATCH--DRVA--SYXCECP--HGRGLLC		
EHS--NFCNEGSNOD--TNPV--NGVATCTCP--SGTGPAC		
ESL--CANPCEHAGKCINTLGSE-----ECQCL--QGYTGPRC		
GVS--NFCNDATCL--DOIG--EFOCMCM--PGYEGVHC		
CAS--SPGTHNGROL--DKIN--EFOCECP--TGFTGHL		
CAS--TEGKNAKCL--DGN--TATGVCT--EYTGTHC		
GDPDP--CHMC--SCK--DGVA--MTOLER--PGWTHHC		
ESS--QPCRLGTCQ--DPDN--AYLGFOL--KGVTHPNC		
CAS--SPG--DSCTCL--DKID--GYFCACE--PGWTHSMC		
CAG--NECHNGCTC--ED--GINGETCRCP--EGVHDPNC		
ENS--NFCVHCARD--SIN--GYKCD--PGWSGTNC		
CES--NFCVNGGTCG--D--MTS--GVVCTCR--EGFSGPNC		
CAS--NPGENKGTG--IDD--VAGYKONCL--EPATGATC		
CAP--SPERNCGECP--QSED--YES--FSCVGETAGARGQTC		
SVL--SPERHGASCO--NTHG--XYRGHCO--AGYSGRNC		
CRPNP-----CHNGGSCT--DGIN--TAFCDCL--PGFRGTFC		
CAS--DP--GRNGANCT--DCVD--SYTCTCP--AGFSGTHC		
CTESS-----CFNGGTCV--DGIN--SFTCLCP--PGFTGSYC		
GDS--RPOHGGTCQ--DG--RGTHRCTCP--QCVTGENC		
GDS--SPCKNGGKCV--QT--HTQYRCECP--SGWTHGYC		
GEVAAQRQGVQVVARLCQHGLCV--DAGN--THHCRCQ--AGYTGSYC		
ESP--SECQNGATCT--DYLG--GYSCKCV--AGYHGVNC		
GLS--HPCNGCTOL--DLPN--TYKCSOP--RGTOGVHC		
ENDEVDPRVRS--PKCFNNGTCTV--DOVG--GYSCTCP--PGFVGPBC		
GLS--NPGDARGTON--CVOR--VNDHCECR--AGHTGRR		
CKG--KPCKNGGTC--VASN--TARGHCKOP--AGFEGATC		
G--GSLRCLNGGTCISGPRSP--TGCLCL--GPFTGPBC		
CL--GGNPGVNGCTCEPTSESPE--YROLCP--AKENGHIC		

Figure 5B

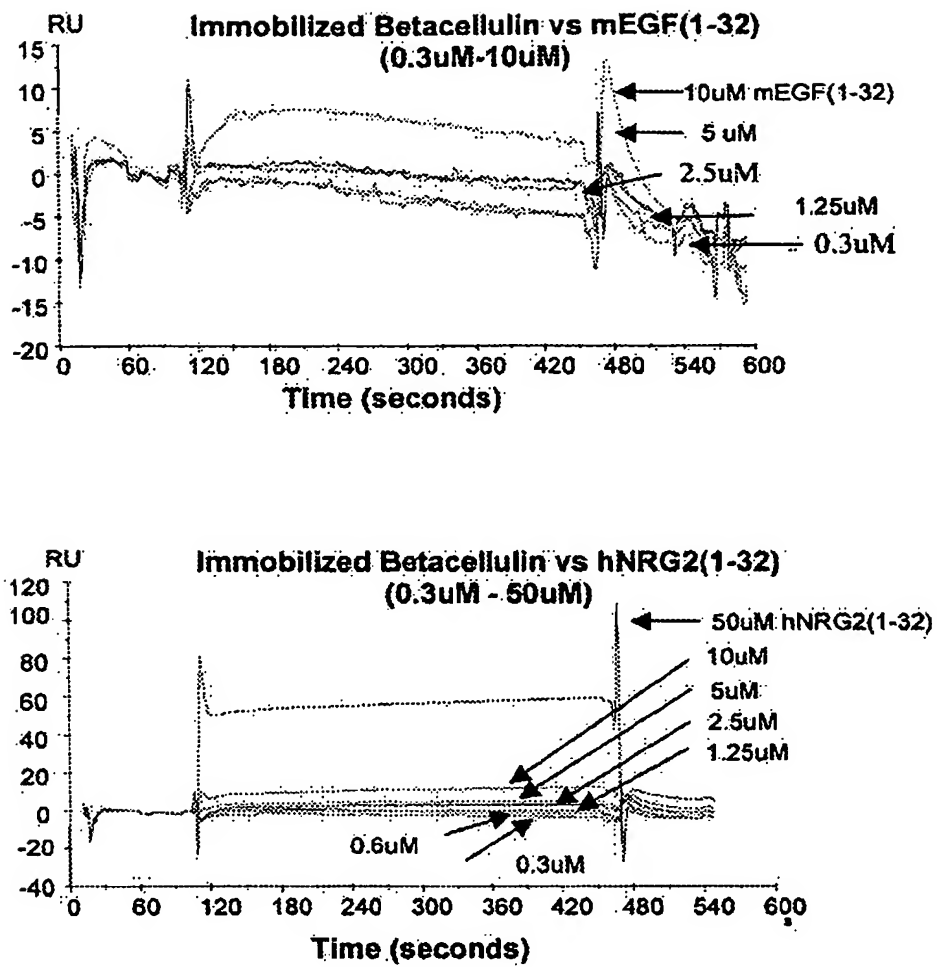


Figure 6